General

Guideline Title

Molecular biomarkers for the evaluation of colorectal cancer: guideline from the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology.

Bibliographic Source(s)

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions for the strength of evidence (Convincing, Adequate, Inadequate, Insufficient) and quality of evidence (High/intermediate, Intermediate/low, Low/insufficient, Insufficient), and strength/type of recommendations (Strong recommendation, Recommendation, Expert consensus opinion, and No recommendation) are provided at the end of the "Major Recommendations" field.

Key Guideline Questions

1. What biomarkers are useful to select patients with colorectal cancer (CRC) for targeted and conventional therapies?
2. How should tissue specimens be processed for biomarker testing for CRC management?
3. How should biomarker testing for CRC management be performed?
4. How should molecular testing of CRC be implemented and operationalized?
5. Are there emerging genes/biomarkers that should be routinely tested in CRC?

Guideline Statements

1. Colorectal carcinoma patients being considered for anti-epidermal growth factor receptor (EGFR) therapy must receive *RAS* (rat sarcoma viral oncogene homolog) mutational testing. Mutational analysis should include *KRAS* (Kirsten rat sarcoma viral oncogene homolog) and *NRAS* (neuroblastoma *RAS* viral [v-ras] oncogene homolog) codons 12, 13 of exon 2; 59, 61 of exon 3; and 117 and 146 of exon 4

("expanded" or "extended" *RAS*) (Type: recommendation; Strength of Evidence: convincing/adequate, benefits outweigh harms; Quality of Evidence: high/intermediate).

2.
   a. *BRAF* (V-raf murine sarcoma viral oncogene homolog B1) p.V600 (*BRAF* c. 1799 [p.V600]) mutational analysis should be performed in colorectal cancer tissue in patients with colorectal carcinoma for prognostic stratification (Type: recommendation, Strength of Evidence: adequate/inadequate, balance of benefits and harms; Quality of Evidence: intermediate/low).
   b. *BRAF* p.V600 mutational analysis should be performed in deficient mismatch repair (MMR) tumors with loss of MLH1 (MutL homolog 1) to evaluate for Lynch syndrome risk. Presence of a *BRAF* mutation strongly favors a sporadic pathogenesis. The absence of *BRAF* mutation does not exclude risk of Lynch syndrome (Type: recommendation, Strength of Evidence: adequate/inadequate, balance of benefits and harms; Quality of Evidence: intermediate/low).

3. Clinicians should order mismatch repair status testing in patients with colorectal cancers for the identification of patients at high risk for Lynch syndrome and/or prognostic stratification (Type: recommendation; Strength of Evidence: adequate/inadequate, balance of benefits and harms; Quality of Evidence: intermediate/low).

4. There is insufficient evidence to recommend *BRAF* c.1799 p.V600 mutational status as a predictive molecular biomarker for response to anti-EGFR inhibitors (Type: no recommendation; Strength of Evidence: insufficient, benefits/harms balance unknown; Quality of Evidence: insufficient).

5. There is insufficient evidence to recommend *PIK3CA* (phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit alpha) mutational analysis of colorectal carcinoma tissue for therapy selection outside of a clinical trial (Type: no recommendation; Strength of Evidence: insufficient, benefits/harms balance unknown; Quality of Evidence: insufficient).
Note: Retrospective studies have suggested improved survival with post-operative aspirin use in patients whose colorectal carcinoma harbors a *PIK3CA* mutation.

6. There is insufficient evidence to recommend PTEN (phosphatase and tensin homolog) analysis (expression by immunohistochemistry [IHC] or deletion by fluorescence in situ hybridization [FISH]) in colorectal carcinoma tissue for patients who are being considered for therapy selection outside of a clinical trial (Type: no recommendation; Strength of Evidence: insufficient, benefits/harms balance unknown; Quality of Evidence: insufficient).

7. Metastatic or recurrent colorectal carcinoma tissues are the preferred specimens for treatment predictive biomarker testing and should be used if such specimens are available and adequate. In their absence, primary tumor tissue is an acceptable alternative, and should be used (Type: expert consensus opinion; Strength of Evidence: inadequate/insufficient, benefits and harms in balance; Quality of Evidence: low).

8. Formalin fixed paraffin embedded tissue is an acceptable specimen for molecular biomarker mutational testing in colorectal carcinoma. Use of other specimens (e.g., cytology specimens) will require additional adequate validation, as would any changes in tissue processing protocols (Type: expert consensus opinion; Strength of Evidence: inadequate/insufficient, benefits and harms in balance; Quality of Evidence: low).

9. Laboratories must use validated colorectal carcinoma molecular biomarker testing methods with sufficient performance characteristics for the intended clinical use. Colorectal carcinoma molecular biomarker testing validation should follow accepted standards for clinical molecular diagnostics tests (Type: strong recommendation; Strength of Evidence: convincing/adequate, benefits outweigh harms; Quality of Evidence: high/intermediate).

10. Performance of molecular biomarker testing for colorectal carcinoma must be validated in accordance with best laboratory practices (Type: strong recommendation; Strength of Evidence: convincing/adequate, benefits outweigh harms; Quality of Evidence: high/intermediate).

11. Laboratories must validate the performance of IHC testing for colorectal carcinoma molecular biomarkers (currently IHC testing for MLH1, MSH2, MSH6, and PMS2) in accordance with best laboratory practices (Type: strong recommendation; Strength of Evidence: convincing/adequate, benefits outweigh harms; Quality of Evidence: high/intermediate).

12. Laboratories must provide clinically appropriate turnaround times and optimal utilization of tissue specimens by using appropriate techniques (e.g., multiplexed assays) for clinically relevant molecular and immunohistochemical biomarkers of colorectal cancer (Type: expert consensus opinion; Strength of Evidence: inadequate/insufficient, benefits and harms in balance; Quality of Evidence: low).

13. Molecular and IHC biomarker testing in colorectal carcinoma should be initiated in a timely fashion based upon the clinical scenario and in accordance with institutionally accepted practices (Type: expert consensus opinion; Strength of Evidence: inadequate/insufficient, benefits and harms in balance; Quality of Evidence: low).
Note: Test ordering can occur on a case-by-case basis or by policies established by the medical staff.

14. Laboratories should establish policies to ensure efficient allocation and utilization of tissue for molecular testing, particularly in small specimens (Type: expert consensus opinion; Strength of Evidence: inadequate/insufficient, benefits and harms in balance; Quality of Evidence: low).

15. Members of the patient's medical team, including pathologists, may initiate colorectal carcinoma molecular biomarker test orders in

accordance with institutionally accepted practices (Type: expert consensus opinion; Strength of Evidence: inadequate/insufficient, benefits and harms in balance; Quality of Evidence: low).

16. Laboratories that require send out of tests for treatment predictive biomarkers should process and send colorectal carcinoma specimens to reference molecular laboratories in a timely manner (Type: expert consensus opinion; Strength of Evidence: inadequate/insufficient, benefits and harms in balance; Quality of Evidence: low).

17. Pathologists must evaluate candidate specimens for biomarker testing to ensure specimen adequacy taking into account tissue quality, quantity, and malignant tumor cell fraction. Specimen adequacy findings should be documented in the patient report (Type: expert consensus opinion; Strength of Evidence: inadequate/insufficient, benefits and harms in balance; Quality of Evidence: low).

18. Laboratories should use colorectal carcinoma molecular biomarker testing methods that are able to detect mutations in specimens with at least 5% mutant allele frequency, taking into account the analytical sensitivity of the assay (limit of detection or LOD) and tumor enrichment (e.g., microdissection) (Type: expert consensus opinion; Strength of Evidence: inadequate/insufficient, benefits and harms in balance; Quality of Evidence: low).

    Note: It is recommended that the operational minimal neoplastic carcinoma cell content tested should be set at least 2 times the assay's LOD.

19. Colorectal carcinoma molecular biomarker results should be made available as promptly as feasible in order to inform therapeutic decision-making, both prognostic and predictive (Type: expert consensus opinion; Strength of Evidence: inadequate/insufficient, benefits and harms in balance; Quality of Evidence: low).

    Note: It is suggested that a benchmark of 90% of reports available within 10 working days from date of receipt in the molecular diagnostics laboratory.

20. Colorectal carcinoma molecular biomarker testing reports should include a results and interpretation section readily understandable by oncologists and pathologists. Appropriate Human Genome Variation Society (HGVS) and Human Genome Organisation (HUGO) nomenclature must be used in conjunction with any historical genetic designations (Type: expert consensus opinion; Strength of Evidence: inadequate/insufficient, benefits and harms in balance; Quality of Evidence: low).

21. Laboratories must incorporate colorectal carcinoma molecular biomarker testing methods into their overall laboratory quality improvement program, establishing appropriate quality improvement monitors as needed to assure consistent performance in all steps of the testing and reporting process. In particular, laboratories performing colorectal carcinoma molecular biomarker testing must participate in formal proficiency testing programs, if available, or an alternative proficiency assurance activity (Type: strong recommendation; Strength of Evidence: convincing/adequate, benefits outweigh harms; Quality of Evidence: high/intermediate).

Definitions

Grades for Strength of Evidence*

Designation	Description	Quality of Evidence
Convincing	High confidence that available evidence reflects true effect. Further research is very unlikely to change the confidence in the estimate of effect.	High/intermediate quality of evidence
Adequate	Moderate confidence that available evidence reflects true effect. Further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate.	Intermediate/low quality of evidence
Inadequate	Little confidence that available evidence reflects true effect. Further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate.	Low/insufficient quality of evidence and Expert Panel uses formal consensus process to reach recommendation
Insufficient	Evidence is insufficient to discern net effect. Any estimate of effect is very uncertain.	Insufficient evidence and Expert Panel uses formal consensus process to reach recommendation

*Adapted from Guyatt GH, Oxman AD, Vist GE, et al: GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. BMJ 336:924-926, 2008, by permission of British Medical Journal (BMJ) Publishing Group Limited.

Grades for Strength of Recommendation*

Designation	Recommendation	Rationale
Strong	Recommend for or against a	Supported by convincing or adequate strength of evidence, high or intermediate

	particular molecular testing practice for colorectal cancer (can include *must* or *should*)	quality of evidence, and clear benefit that outweighs any harms
recommendation		
Recommendation	Recommend for or against a particular molecular testing practice for colorectal cancer (can include *should* or *may*)	Some limitations in strength of evidence (adequate or inadequate) and quality of evidence (intermediate or low), balance of benefits and harms, values, or costs, but panel concludes that there is sufficient evidence and/or benefit to inform a recommendation
Expert consensus opinion	Recommend for or against a particular molecular testing practice for colorectal cancer (can include *should* or *may*)	Serious limitations in strength of evidence (inadequate of insufficient), quality of evidence (intermediate or low), balance of benefits and harms, values, or costs, but panel consensus is that a statement is necessary
No recommendation	No recommendation for or against a particular molecular testing practice for colorectal cancer	Insufficient evidence or agreement of the balance of benefits and harms, values, or costs to provide a recommendation

*Data derived from Guyatt GH, Oxman AD, Vist GE, et al: GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. BMJ 336:924-926, 2008.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Colorectal cancer (CRC)

Guideline Category

Diagnosis

Evaluation

Technology Assessment

Clinical Specialty

Gastroenterology

Medical Genetics

Oncology

Pathology

Intended Users

Clinical Laboratory Personnel

Health Care Providers

Other

Patients

Guideline Objective(s)

- To develop an evidence-based guideline to help establish standard molecular biomarker testing, guide targeted therapies, and advance personalized care for patients with colorectal cancer (CRC)
- To address the following key questions:
  - What biomarkers are useful to select patients with CRC for targeted and conventional therapies?
  - How should tissue specimens be processed for biomarker testing for CRC management?
  - How should biomarker testing for CRC management be performed?
  - How should molecular testing of CRC be implemented and operationalized?
  - Are there emerging genes/biomarkers that should be routinely tested in CRC?

Target Population

Patients with colorectal cancer (CRC) being considered for treatment with anti-epidermal growth factor receptor (EGFR) inhibitors or conventional chemotherapy

Interventions and Practices Considered

1. Biomarker testing
   - *KRAS* (Kirsten rat sarcoma viral oncogene homolog) mutational analysis
   - *NRAS* (neuroblastoma RAS viral [v-ras] oncogene homolog) mutational analysis
   - *BRAF* (V-raf murine sarcoma viral oncogene homolog B1) mutational analysis
   - Evaluation of DNA mismatch repair (MMR)/microsatellite instability (MSI) status
   - *PIK3CA* (phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit alpha) mutational analysis (*insufficient evidence to recommend*)
   - *PTEN* (phosphatase and tensin homolog) [expression by immunohistochemistry (IHC) or deletion by fluorescence in situ hybridization (FISH)] (*insufficient evidence to recommend*)
   - *MLH1* (MutL homolog 1) methylation levels
2. Tissue specimen processing for biomarker testing
3. Use of validated colorectal carcinoma molecular biomarker testing methods
4. Validation of IHC testing performance
5. Timeliness of testing
6. Coordination and organization of testing
7. Ensuring accuracy and comprehensibility of testing reports

Major Outcomes Considered

- Survival (overall, disease-free survival, progression-free survival, recurrence-free)
- Time to recurrence
- Response to therapy (complete and partial response)
- Performance characteristics of laboratory testing assays
  - Percent mutation
  - Concordance of testing methods
  - Sensitivity/specificity of testing methods
  - Concordance of detected mutations between primary and metastatic mutations (number [%] of cases with mutations versus number of cases with no mutations in the gene of interest)
  - Concordance of mutations (synchronous primary versus metastatic, metachronous primary versus metastatic, between synchronous metastases, between metachronous metastases)

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search and Selection

A comprehensive search for literature was performed in MEDLINE using the OvidSP (August 1, 2013) and PubMed (September 17, 2013) interfaces. The initial MEDLINE search encompassed the publication dates of January 1, 2008, through August 1, 2013 (OvidSP), and January 1, 2008, through September 17, 2013 (PubMed). A supplemental literature search was performed using Scopus (September 25, 2013) to identify relevant articles published between January 1, 2008, and September 25, 2013, in journals not indexed in MEDLINE. The literature search of the electronic databases involved two separate searches in each database, the first using Medical Subject Headings (MeSH) terms and keywords for the concepts "colorectal cancer," "biomarkers," "treatment," and "treatment outcomes" and the second using terms for the concepts "colorectal cancer," "biomarkers," and "laboratory methods." Limits were set for human studies published in English, and a publication filter was applied to exclude lower levels of evidence such as letters, commentaries, editorials, and case reports. The Ovid search was rerun on February 12, 2015, to identify articles published since August 1, 2013.

In addition to the searches of electronic databases, an Internet search of international health organizations, the National Guideline Clearinghouse, and Guidelines International Network was conducted for existing relevant guidelines or protocols. Guidelines were included if they were published since 2008 in English. The proceedings of the meetings of American Association of Clinical Oncology (ASCO) and ASCO Gastrointestinal Cancers Symposium, European Society for Medical Oncology, and the American Association for Cancer Research from 2012 and 2013 were also searched for relevant abstracts.

A focused examination of all systematic reviews retrieved by the initial literature search and retained after full-text review was performed to identify primary research studies not already included. In addition, recommendations from the Expert Panel were reviewed, and the reference lists of all articles deemed eligible for inclusion were scanned for relevant reports. The results of all searches were combined and deduplicated.

Detailed information regarding the literature search strategy can be found in the supplemental digital content (see the "Availability of Companion Documents" field).

Eligible Study Designs

Practice guidelines, consensus documents, systematic reviews, meta-analyses, randomized controlled trials, comparative studies, reviews, and evaluation studies were eligible for inclusion. In addition to journal articles, the search identified meeting abstracts.

Inclusion Criteria

Published studies were selected for full-text review if they met each of the following criteria:

1. Patients with colorectal or rectal cancer with a pathology diagnosis of adenocarcinoma or adenocarcinoma with neuroendocrine differentiation, either primary or metastatic
2. Patients of all ages
3. Patients with cancer of any invasive stage (T1-T4)
4. Biomarker testing such as *KRAS* (Kirsten rat sarcoma viral oncogene homolog), deoxyribonucleic acid (DNA) mismatch repair/microsatellite instability (MMR/MSI), *BRAF* (V-raf murine sarcoma viral oncogene homolog B1), NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog), *PIK3CA* (phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit alpha), *PTEN* (phosphatase and tensin homolog), *MLH1* (MutL homolog 1) methylation, or gene expression profiles
5. Comparative studies
6. Human studies
7. Studies published in English

Exclusion Criteria

1. All other tumor primaries and types (i.e., noncolorectal or nonrectal cancers, tumor types other than adenocarcinoma or adenocarcinoma with neuroendocrine differentiation)
2. Patients with noninvasive tumors (i.e., intraepithelial, dysplasia, in situ, polyps without carcinoma)
3. Studies of colorectal cancers (CRCs) without biomarker testing, novel biomarkers—for example, VEG-F (vascular endothelial growth factor), XRCC1 (X-ray repair complementing defective repair in Chinese hamster cells 1), IGF (insulin-like growth factor), ERCC (excision repair cross-complementing rodent repair deficiency, complementation group 1), micro-ribonucleic acid (RNA), TYMS (thymidylate synthetase), GCC (guanylyl cyclase C), LINE (long interspersed nucleotide element) methylation, CIMP (CpG island methylator phenotype), HER2 (V-erb-b2 erythroblastic leukemia viral oncogene homolog 2), CIN (chromosomal instability) status LOH (loss of heterozygosity), and germline (genetics only) testing
4. Non–English-language articles
5. Animal studies
6. Studies published prior to 2002
7. Noncomparative studies, letters, commentaries, or editorials
8. Studies that did not address at least one of the defined inclusion criteria
9. Studies with fewer than 50 patients per comparison arm

Outcomes of Interest

The primary outcomes of interest included survival outcomes and performance characteristics of laboratory testing assays. Survival outcomes included overall survival (OS), disease-free survival (DFS), progression-free survival (PFS), recurrence-free survival, time to recurrence, response to therapy (e.g., complete and partial response). Laboratory data and test performance characteristics included percent mutation, concordance of testing methods, sensitivity of testing methods, specificity of testing methods, concordance of detected mutations between primary and metastatic mutations (number [%] of cases with mutations versus number of cases with no mutations in the gene of interest), and concordance of mutations (synchronous primary versus metastatic, metachronous primary versus metastatic, between synchronous metastases, between metachronous metastases).

Number of Source Documents

A total of 4,197 studies met the search term requirements. A total of 123 articles were included for data extraction. Excluded articles were available as discussion or background references. (refer to Figure 1 in the supplemental digital content [see the "Availability of Companion Documents" field] for the Literature Review Flow Diagram).

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Grades for Strength of Evidence*

Designation	Description	Quality of Evidence
Convincing	High confidence that available evidence reflects true effect. Further research is very unlikely to change the confidence in the estimate of effect.	High/intermediate quality of evidence
Adequate	Moderate confidence that available evidence reflects true effect. Further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate.	Intermediate/low quality of evidence
Inadequate	Little confidence that available evidence reflects true effect. Further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate.	Low/insufficient quality of evidence and Expert Panel uses formal consensus process to reach recommendation
Insufficient	Evidence is insufficient to discern net effect. Any estimate of effect is very uncertain.	Insufficient evidence and Expert Panel uses formal consensus process to reach recommendation

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Quality Assessment

An assessment of the quality of the evidence was performed for all retained studies following application of the inclusion and exclusion criteria by the methodologist. Using this method, studies deemed to be of low quality would not be excluded from the systematic review but would be retained and their methodologic strengths and weaknesses discussed where relevant. Studies would be assessed by confirming the presence of items related to both internal and external validity, which are all associated with methodologic rigor and a decrease in the risk of bias. The quality assessment of the studies was performed by determining the risk of bias by assessing key indicators, based on study design, against known criteria. (Refer to the supplemental digital content [see the "Availability of Companion Documents" field]) for detailed discussion of the quality assessment.)

For strength of the evidence, the panel considered the level of evidence, as well as its quantity and quality of included studies. The level of evidence was based on the study design as follows:

- Level I - evidence from systematic reviews or clinical practice guidelines of appropriate level II studies
- Level II - evidence from good-quality, randomized, controlled trials
- Level III - evidence from low-quality comparative studies (e.g., prospective cohort studies, retrospective cohort studies)
- Level IV - evidence from studies without a comparator (e.g., case reports, case series, narrative reviews)

In general, level I and II evidence is considered most appropriate to answer clinical questions, but in the absence of such high-quality evidence, the panel considered data from lower quality studies. The quantity of evidence refers to the number of studies and number of cases included for each outcome in the recommendation. The quality of studies reflects how well the studies were designed to eliminate bias and threats to validity.

The appropriateness of the study design and data collected, relevance and clarity of findings, and adequacy of conclusions were evaluated. Each study was assessed individually (refer to the supplemental digital content for individual assessments and results) and then summarized by study type. Components such as generalizability and applicability were also considered when determining the strength of evidence. A summary of the overall quality of the evidence was given considering the evidence in totality. Ultimately, the designation (i.e., rating or grade) of the strength of evidence is a judgment by the Expert Panel of its level of confidence that the evidence from the studies informing the recommendations reflects true effect (see the "Rating Scheme for the Strength of the Evidence" field for the grades for strength of evidence).

Methods Used to Formulate the Recommendations

Expert Consensus (Nominal Group Technique)

Description of Methods Used to Formulate the Recommendations

Panel Composition

The American Society for Clinical Pathology (ASCP), the College of American Pathologists (CAP) Pathology and Laboratory Quality Center (the Center), the Association for Molecular Pathology (AMP), and the American Society of Clinical Oncology (ASCO) convened an Expert Panel consisting of practicing pathologists, oncologists, geneticists, and a biostatistician with expertise and experience in molecular biomarker testing and targeted therapies for colorectal cancer (CRC). The ASCP, CAP, AMP, and ASCO jointly approved the appointment of the project, co-chairs, and Expert Panel members. In addition, a methodologist experienced in systematic review and guideline development consulted with the panel throughout the project.

Assessing the Strength of Recommendations

Development of recommendations requires that the panel review the identified evidence and make a series of key judgments (using procedures described in the supplemental digital content [see the "Availability of Companion Documents" field]). Grades for strength of recommendations were developed by the College of American Pathologists (CAP) Pathology and Laboratory Quality Center and are described in "Rating Scheme of the Strength of the Recommendations" field.

The panel convened 14 times (11 teleconference webinars and three face-to-face meetings) from July 27, 2013, through September 24, 2015, to develop the scope, draft recommendations, review and respond to solicited feedback, and assess the quality of evidence that supports the final recommendations. Additional work was completed via electronic mail. An open comment period was held from March 30, 2015, through April 22, 2015, during which draft recommendations were posted on the AMP Web site. Twenty-one guideline statements had an agreement ranging from 60% to 94% for each statement from the open-comment period participants (refer to Outcomes section in the supplemental digital content [see the "Availability of Companion Documents" field] for full details).

The Web site received a total of 248 comments. Teams of three to four Expert Panel members were assigned three to five draft recommendations to review all comments received and provide an overall summary to the rest of the panel. Following panel discussion and the final quality of evidence assessment, the panel members determined whether to maintain the original draft recommendation as is, revise it with minor language change, or consider it as a major recommendation change. The Expert Panel modified eight draft statements based on the feedback during the open-comment period and the considered judgment process. Resolution of all changes was obtained by majority consensus of the panel using nominal group technique (rounds of email discussion and multiple edited recommendations) among the panel members. The final recommendations were approved by the Expert Panel with a formal vote. The panel considered the risks and benefits throughout the judgment process.

Rating Scheme for the Strength of the Recommendations

Grades for Strength of Recommendation*

Designation	Recommendation	Rationale
Strong recommendation	Recommend for or against a particular molecular testing practice for colorectal cancer (can include *must* or *should*)	Supported by convincing or adequate strength of evidence, high or intermediate quality of evidence, and clear benefit that outweighs any harms
Recommendation	Recommend for or against a particular molecular testing practice for colorectal cancer (can include *should* or *may*)	Some limitations in strength of evidence (adequate or inadequate) and quality of evidence (intermediate or low), balance of benefits and harms, values, or costs, but panel concludes that there is sufficient evidence and/or benefit to inform a recommendation
Expert consensus opinion	Recommend for or against a particular molecular testing practice for colorectal cancer (can include *should* or *may*)	Serious limitations in strength of evidence (inadequate of insufficient), quality of evidence (intermediate or low), balance of benefits and harms, values, or costs, but panel consensus is that a statement is necessary
No recommendation	No recommendation for or against a particular molecular testing practice for colorectal cancer	Insufficient evidence or agreement of the balance of benefits and harms, values, or costs to provide a recommendation

*Data derived from Guyatt GH, Oxman AD, Vist GE, et al: GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. BMJ 336:924-926, 2008.

Cost Analysis

Formal cost analysis or cost-effectiveness was not performed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

A public open comment period was held from March 30 through April 22, 2015. Twenty-one draft statements (8 recommendations, 10 expert consensus opinions, and 3 no recommendation) were posted online on the Association for Molecular Pathology (AMP) Web site. The open comment period was publicized via joint society communications announcements to the societies that were deemed to have interest (see the Supplemental Methodology [see the "Availability of Companion Documents" field] for the full list of societies).

Each organization instituted a review process to approve the guideline. The American Society for Clinical Pathology (ASCP) assigned the review of the guideline to a Special Review Panel. For the College of American Pathologists (CAP), an independent review panel (IRP) representing the Council on Scientific Affairs was assembled to review and approve the guideline. The IRP was masked to the Expert Panel and vetted through the conflict of interest process. The AMP approval process required the internal review of an independent panel led by the Publications and Communications Committee Chair and Executive Committee approval. The American Society for Clinical Pathology (ASCO) approval process required the review and approval of the Clinical Practice Guidelines Committee.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Evidence supports mutational testing of specific genes in the epidermal growth factor receptor (EGFR) signaling pathway, since they provide clinically actionable information for targeted therapy of colorectal cancer (CRC) with anti-EGFR monoclonal antibodies. Mutations in some of the biomarkers have clear prognostic value (*BRAF* [V-raf murine sarcoma viral oncogene homolog B1], MMR [mismatch repair]), and at least two (*KRAS* [Kirsten rat sarcoma viral oncogene homolog] and *NRAS* [neuroblastoma *RAS* (rat sarcoma viral oncogene homolog) viral (v-ras) oncogene homolog]) have relatively strong evidence as negative predictors of benefit to anti-EGFR therapies and should be used to guide the use of these agents. *BRAF* mutations are consistently associated with poor outcomes in patients with metastatic CRC, including those who relapse after adjuvant therapy. Patients with localized colon cancer and dMMR (deficient mismatch repair) have improved outcomes. Emerging data indicate that MMR status may have predictive value in some settings, specifically in patients with advanced disease being considered for anti–programmed cell death protein-1 (anti-PD-1)/anti–programmed cell death protein-1 (PD-L1) therapy.

Potential Harms

- Proper validation of colorectal cancer (CRC) biomarker testing is important to ensure appropriate patient care. If validation is inadequate, this can lead to erroneous results and improper diagnosis, prognosis, and/or therapeutic intervention. For example, with regard to *RAS* (rat sarcoma viral oncogene homolog) testing, a false-positive result would lead to an improper withholding of therapy, whereas a false-negative result would lead to distribution of an ineffective therapy, resulting in increased costs and unnecessary side effects.
- Pathologists evaluating tissue section for biomarker evaluation should also be aware that necrosis and tissue degeneration can lead to erroneous results, and foci demonstrating significant necrosis should be avoided for molecular testing. Any amount of necrosis in the sample selected for biomarker testing should be estimated and documented.

Qualifying Statements

Qualifying Statements

Guideline Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by the American Society for Clinical Pathology (ASCP), the College of American Pathologists (CAP) Pathology and Laboratory Quality Center (the Center), the Association for Molecular Pathology (AMP), and the American Society of Clinical Oncology (ASCO) to assist providers in clinical decision making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO provides this information on an "as is" basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.

Implementation of the Guideline

Description of Implementation Strategy

Dissemination Plans

Final dissemination of the guideline will be a joint process between the four organizations (American Society for Clinical Pathology [ASCP], College of American Pathologists [CAP], Association for Molecular Pathology [AMP], and the American Society of Clinical Oncology [ASCO]). There are plans to host a resource page which will include a link to the manuscript and supplement, summary of the recommendations, social media as well as patient information guides. The guideline will be promoted and presented at various society meetings.

For additional information on the ASCO implementation strategy, please see the ASCO Web site _____.

Implementation Tools

Patient Resources

Quick Reference Guides/Physician Guides

Resources

Slide Presentation

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Sepulveda AR, Hamilton SR, Allegra CJ, Grody W, Cushman-Vokoun AM, Funkhouser WK, Kopetz SE, Lieu C, Lindor NM, Minsky BD, Monzon FA, Sargent DJ, Singh VM, Willis J, Clark J, Colasacco C, Rumble RB, Temple-Smolkin R, Ventura CB, Nowak JA. Molecular biomarkers for the evaluation of colorectal cancer: guideline from the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology. J Clin Oncol. 2017 May 1;35(13):1453-86. [152 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2017 May 1

Guideline Developer(s)

American Society for Clinical Pathology - Professional Association

American Society of Clinical Oncology - Medical Specialty Society

Association for Molecular Pathology - Medical Specialty Society

College of American Pathologists - Medical Specialty Society

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Guideline Committee

Expert Panel

Composition of Group That Authored the Guideline

Expert Panel Membership: Antonia Sepulveda, MD, PhD (*co-chair, Association for Molecular Pathology [AMP]*), Department of Pathology and Cell Biology, Columbia University, New York, NY; Stanley R. Hamilton, MD, PhD (*co-chair, College of American Pathologists [CAP]*), Department of Pathology, University of Texas MD Anderson Cancer Center, Houston, TX; Carmen Allegra, MD (*co-chair, American Society*

of Clinical Oncology [ASCO]), Division of Hematology and Oncology, University of Florida Medical Center, Gainesville, FL; Wayne Grody, MD, PhD (*co-chair, American Society for Clinical Pathology [ASCP]*), Departments of Pathology and Laboratory Medicine, UCLA Medical Center, Los Angeles, CA; Allison Cushman-Vokoun, MD, PhD (ASCP), Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, NE; William K. Funkhouser, MD, PhD (AMP), Department of Pathology and Laboratory Medicine, University of North Carolina School of Medicine, Chapel Hill, NC; Scott Kopetz, MD, PhD (ASCO), Department of Gastrointestinal (GI) Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX; Christopher Lieu, MD (ASCO), Division of Medical Oncology, University of Colorado Denver School of Medicine, Denver, CO; Noralane Lindor, MD (AMP), Department of Medical Genetics, Mayo Clinic, Scottsdale, AZ; Bruce Minsky, MD (CAP), Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, TX; Federico Monzon, MD (AMP), Castle Biosciences, Friendswood, TX; Daniel Sargent, PhD (CAP), Department of Health Sciences Research, Mayo Clinic, Rochester, MN; Veena Singh, MD (ASCP), Biocept, Inc,, San Diego, California; Joseph Willis, MD (ASCP), Department of Pathology, Case Western Reserve University, Cleveland, OH; Jan Nowak, MD, PhD (CAP), Department of Molecular Pathology, Roswell Park Cancer Institute, Albany, NY

Staff: R. Bryan Rumble, MSc, American Society of Clinical Oncology; Jennifer Clark, SCT(ASCP)CM, MBCM, American Society for Clinical Pathology; Carol Colasacco, MLIS, College of American Pathologists; Robyn Temple-Smolkin, PhD, HCLD, Association for Molecular Pathology; Christina B. Ventura, MT(ASCP), College of American Pathologists

Financial Disclosures/Conflicts of Interest

Prior to acceptance on the expert or advisory panel, potential members completed a joint guideline conflict of interest (COI) disclosure process, whose policy and form (in effect July 2011) require disclosure of material financial interest in, or potential for benefit of significant value from, the guideline's development or its recommendations 12 months prior through the time of publication. The potential members completed the COI disclosure form, listing any relationship that could be interpreted as constituting an actual, potential, or apparent conflict. All project participants were required to disclose conflicts prior to beginning and continuously throughout the project's timeline.

Authors' Disclosures of Potential Conflicts of Interest

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The information below reflects disclosures that were collected and reviewed by the College of American Pathologists, the American Society for Clinical Pathology, and the American Society of Clinical Oncology. The disclosures that appear in the individual journals of the societies may vary based on journal-specific policies and procedures.

Antonia R. Sepulveda
No relationship to disclose

Stanley R. Hamilton
Consulting or Advisory Role: Intervention Insights, Amgen, Palmetto GBA, HalioDx, Fred Hutchinson Cancer Research Center

Carmen J. Allegra
Honoraria: Bristol-Myers Squibb (I)

Wayne Grody
Stock or Other Ownership: Merck, Amgen
Consulting or Advisory Role: Advanced Medical Reviews
Expert Testimony: Par Pharmaceuticals

Allison M. Cushman-Vokoun
No relationship to disclose

William K. Funkhouser
No relationship to disclose

Scott E. Kopetz
Stock or Other Ownership: MolecularMatch

Consulting or Advisory Role: Amgen, Roche, Merrimack, Bayer, Taiho Pharmaceutical, Sanofi, Array BioPharma, Genentech, MolecularMatch

Research Funding: Amgen, Sanofi, Biocartis, Guardant Health, Array BioPharma, Bayer, Genentech/Roche, MolecularMatch, Taiho Pharmaceutical

Christopher Lieu
Consulting or Advisory Role: Merrimack, Merck

Noralane M. Lindor
Consulting or Advisory Role: Lumena Pharmaceuticals (I), Gilead Sciences (I), Intercept Pharmaceuticals (I)
Patents, Royalties, Other Intellectual Property: Royalties as editor for section in UpToDate. Royalties as editor for section in UpToDate (I)
Travel, Accommodations, Expenses: Intercept Pharmaceuticals (I)

Bruce D. Minsky
Other Relationship: American Society for Radiation Oncology, MD Anderson Physicians Network

Federico A. Monzon
Employment: InVitae, Castle Biosciences
Leadership: Castle Biosciences
Stock or Other Ownership: InVitae, Castle Biosciences

Daniel J. Sargent
Consulting or Advisory Role: Abbvie, Acerta Pharma, ARIAD, Astellas Pharma, AstraZeneca/MedImmune, Biothera, Celldex, Exelixis, Genentech, Incyte, Kyowa Hakko Kirin, Medivation, Merck, Merrimack, Nektar, Novartis, Pharmacyclics, Pique, Spiration, Xbiotech
Research Funding: Celgene (Inst), Roche/Genentech (Inst)
Travel, Accommodations, Expenses: Celgene

Veena M. Singh
Employment: Biocept
Leadership: Biocept
Stock or Other Ownership: Biocept
Consulting or Advisory Role: bioTheranostics
Travel, Accommodations, Expenses: Biocept

Joseph Willis
Patents, Royalties, Other Intellectual Property: PCT/US2008/010395: CWRU, Markowitz, Willis, Dawson, the disclosure provides, among other things, molecular markers for diagnosing neoplasias or categorizing the neoplastic state of a patient. PCT/US2012/043834. CWRU, Markowitz, Willis, Chak, Leidner, this application describes methods and compositions for detecting and treating vimentin-associated neoplasia. Submission Case Western Reserve University: Drs Amitabh Chak, Sanford Markowitz, Joseph Willis, design for an esophageal sampling device. Submission Case Western Reserve University: Drs Delaney, Madabhushi, Paspulati, Viswanath, Willis, Computational Scalpel: Treatment Planning of Rectal Cancer with Image Analytics.

Jennifer Clark
No relationship to disclose

Carol Colasacco
No relationship to disclose

R. Bryan Rumble
Employment: Park Lane Terrace (I)

Robyn Temple-Smolkin
No relationship to disclose

Christina B. Ventura
No relationship to disclose

Jan A. Nowak
Employment: OmniSeq
Leadership: OmniSeq

Stock or Other Ownership: OmniSeq

Travel, Accommodations, Expenses: OmniSeq

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Journal of Clinical Oncology Web site [   ].

Availability of Companion Documents

The following are available:

- Molecular biomarkers for the evaluation of colorectal cancer: guideline from the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology. Supplemental digital content. Methodology. Alexandria (VA): American Society of Clinical Oncology; 2017. 41 p. Available from the American Society of Clinical Oncology (ASCO) Web site [   ].
- Molecular biomarkers for the evaluation of colorectal cancer: guideline from the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology. Infographic. Alexandria (VA): American Society of Clinical Oncology; 2017. 1 p. Available from the ASCO Web site [   ].
- Molecular biomarkers for the evaluation of colorectal cancer: guideline from the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology. Slide set. Alexandria (VA): American Society of Clinical Oncology; 2017. 15 p. Available from the ASCO Web site [   ].
- Molecular biomarkers for the evaluation of colorectal cancer: guideline from the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology. Summary of recommendations. Alexandria (VA): American Society of Clinical Oncology; 2017. 4 p. Available from the ASCO Web site [   ].

Patient Resources

The following are available:

- Colorectal cancer. Patient information. 2017. Available from the Cancer.Net Web site [   ].
- Tumor marker tests. Patient information. 2017. Available from the Cancer.Net Web site [   ].
- Understanding targeted therapy. 2017. Available from the Cancer.Net Web site [   ].

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

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